

Tetrathiafulvalene: A Convenient Large-Scale (20 g) Synthesis

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A cheap, high yielding large-scale (20 g) synthesis of tetrathiafulvalene is reported.

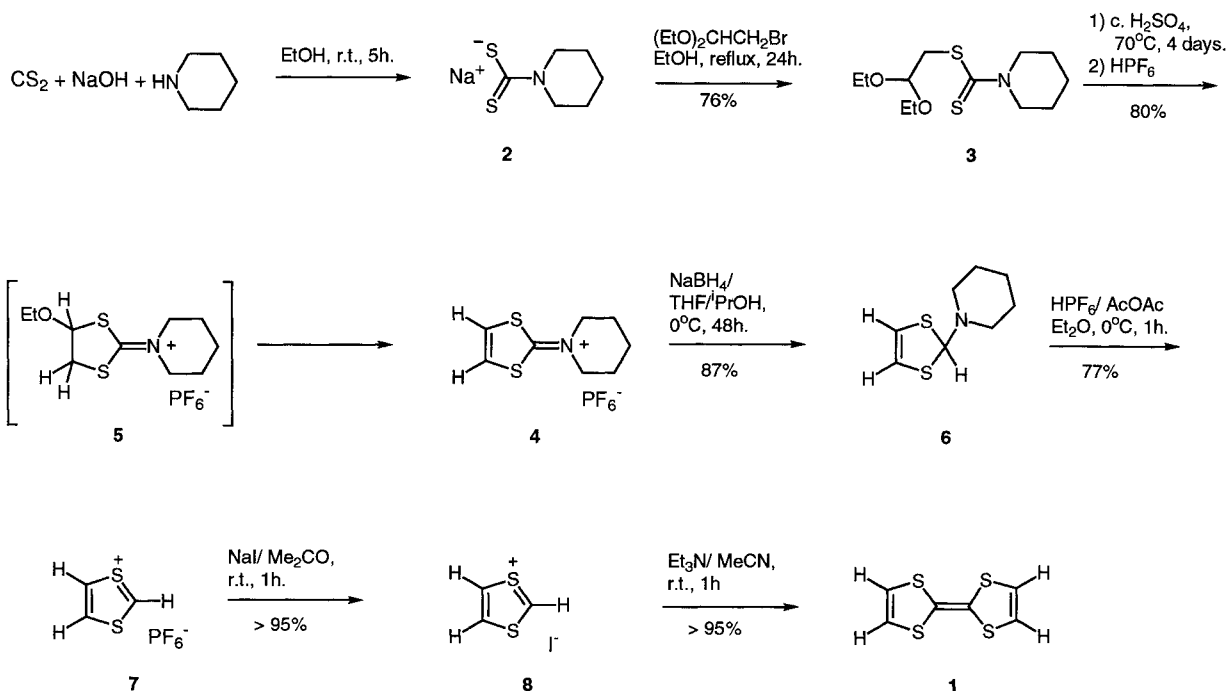
Since its discovery,¹ the π -electron donor molecule tetrathiafulvalene (TTF, **1**) and its derivatives have been central to the development of organic metals and organic superconductors.² From this viewpoint, and within the wider context of exploiting TTF as a building block in supramolecular chemistry,³ much attention has focussed on the synthesis of substituted TTFs via trapping reactions of lithiated TTFs.⁴ More recently, the electron donor properties of TTF have been exploited in a new direction in the trapping of translocated radicals.⁵

During our investigations⁶ of the chemistry of TTF (**1**) we have repeatedly found literature routes for its synthesis (or for the synthesis of key intermediates)^{7–12} to be capricious and often malodorous. Furthermore, commercial TTF is very expensive.¹³ We have, therefore, developed a cheap, reliable large-scale synthesis of TTF by modifications of reported literature procedures.^{9–11} A notable practical advantage of our route is that no chromatography is required at any stage and ca. 20 g batches of TTF can be conveniently prepared.

Our synthetic route to TTF (**1**) is outlined in the Scheme. Treatment of sodium piperidine-1-carbodithioate (**2**) with bromoacetaldehyde diethyl acetal in refluxing ethanol affords formylmethyl piperidine-1-carbodithioate diethyl acetal (**3**) (76% yield).⁹ Sulfuric acid induced cyclisation of **3** at ca. 70 °C for 96 hours affords the desired iminium

salt **4**,⁹ isolated as the hexafluorophosphate salt (80% yield). As noted by Guziec et al.,⁹ if this cyclisation is attempted at lower temperatures, then only iminium salt **5** is isolated, and if the reaction (on a 2 molar scale) is terminated early, significant quantities of iminium salt **5** are also observed in the reaction product (e.g., after 48 hours, iminium salts **4** and **5** are present in ca. 1:1 ratio, as judged by ¹H NMR). Reduction of iminium salt **4** occurs with sodium borohydride in anhydrous THF/propan-2-ol at 0 °C to afford compound **6**^{10,11} and subsequent deamination of **6** is achieved by slow addition of an ethereal solution of **6** to anhydrous hexafluorophosphoric acid (formed by addition of aqueous hexafluorophosphoric acid to anhydrous acetic anhydride) at 0 °C, precipitating the salt **7** as a white solid.¹¹ Purification of salt **7** is most easily achieved by conversion to its iodide salt **8**: thus, addition of an acetone solution of sodium iodide to an acetone solution of salt **7** precipitates directly salt **8** (63% yield based on iminium salt **4**). TTF (**1**) is prepared in virtually quantitative yield by base-induced coupling of salt **8** using the method described by Melby et al.⁷ without modification. The overall yield of this 5-step sequence of reactions is >37%, providing batches of ca. 20 g of TTF **1**.

In conclusion, we have detailed a convenient, cheap, high yielding five-step synthesis of TTF (**1**).¹⁴ In developing the synthetic sequence to TTF outlined in the Scheme, it should be noted that we have also made available for the first time bulk quantities of compounds **4** and **8**,



Scheme

which are widely used in the preparation of TTF derivatives, e.g. (i) compound **4** is a key reagent in the selective synthesis of unsymmetrical TTF derivatives developed by Lerstrup et al.¹⁰ and Fourmigué et al.¹⁵ and (ii) compound **8** is a precursor to 2-dialkoxyphosphinyl-1,3-dithiole,¹⁶ which is used extensively in the synthesis of 1,3-dithiol-2-ylidene derivatives.¹⁷

¹H NMR and ¹³C NMR spectra were obtained on a Bruker AC 250 spectrometer operating at 250.134 MHz and 62.900 MHz, respectively. Melting points were obtained on a Kofler hot-stage microscope apparatus and are uncorrected. All reagents were of commercial quality and dried where necessary using standard procedures.

Formylmethyl Piperidine-1-carbodithioate Diethyl Acetal (**3**):

To a mechanically stirred ice-cooled solution of piperidine (198 mL, 2 mol) in EtOH (750 mL) in a 2L flask fitted with a dropping funnel and reflux condenser were added NaOH pellets (80 g, 2 mol) portionwise over ca. 15 min. CS₂ (120 mL, 2 mol) was added dropwise over ca. 1 h and stirring continued for 1 h at 0 °C (during this time the solution turned yellow, and a white precipitate of sodium dithiocarbamate **2** formed), and then at reflux for 3 h. Bromoacetaldehyde diethyl acetal (300 mL, 2 mol) was added dropwise over ca. 0.5 h (forming a wine-red solution) and the mixture refluxed for a further 24 h. After cooling, H₂O (1.0 L) was added and the mixture extracted with CH₂Cl₂ (4 × 350 mL), the organic extracts combined, washed with H₂O (3 × 250 mL), dried (MgSO₄) and evaporated in vacuo to afford a wine-red oil which solidified on standing. Two recrystallisations from hexane (with cooling in a freezer) afforded the product **3** (421 g, 76 %) as an off-white solid of sufficient purity for further reaction. An analytical sample was obtained by repeated recrystallisation from hexane, affording the product as an off-white solid; mp 46–47 °C (Lit.⁹ mp 46.5–48 °C).

¹H NMR (CDCl₃/TMS): δ = 4.69 (1 H, t, *J* = 5.4 Hz), 4.29 (2 H, br s), 3.92 (2 H, br s), 3.78–3.62 (2 H, m), 3.59 (4 H, q, *J* = 7.1 Hz), 1.71 (6 H, br s), 1.23 (6 H, t, *J* = 7.1 Hz).

¹³C NMR (CDCl₃/TMS): δ = 195.5, 101.7, 62.9, 53.4, 51.6, 40.5, 26.0, 25.9, 24.6, 15.6.

2-Piperidino-1,3-dithiolium Hexafluorophosphate (**4**):

Compound **3** (415 g, 1.5 mol) was added portionwise over ca. 2 h to a stirred, ice-cooled solution of concd H₂SO₄ (350 mL). After the addition was complete, the reaction temperature was raised to ca. 70 °C and maintained at this temperature for 4 d. After cooling, the mixture was poured slowly into ice-cooled, vigorously stirred H₂O (1.5 L) containing HPF₆ (60 wt% in H₂O, 365 g, 1.5 mol) forming a heavy white precipitate. The solid was collected by filtration and washed with H₂O (2.5 L). For purification, the solid was dissolved in CH₂Cl₂ (ca. 2.5 L) and the organic phase washed sequentially with H₂O (500 mL), satd NaHCO₃ (500 mL) and H₂O (500 mL), dried (MgSO₄) and evaporated in vacuo to the point of crystallisation, whereupon Et₂O (750 mL) was added precipitating the product **4** as a grey-white solid, which was collected by filtration and washed with Et₂O (300 mL) (400 g, 80%). Recrystallisation, if required, may be achieved by dissolution in CH₂Cl₂ and addition of Et₂O; mp 162–163 °C (Lit.¹¹ mp 168 °C).

¹H NMR (acetone-*d*₆/TMS): δ = 7.64 (2 H, s), 3.96 (4 H, t, *J* = 5.9 Hz), 1.96 (4 H, m), 1.80 (2 H, m).

¹³C NMR (acetone-*d*₆/TMS): δ = 192.1, 128.0, 60.6, 28.3, 25.1.

2-Piperidino-1,3-dithiole (**6**):

To a mechanically stirred suspension of salt **4** (125 g, 0.38 mol) in anhyd THF/*i*-PrOH (1:1 v/v, 1.0 L) at 0 °C under N₂ was added portionwise finely ground NaBH₄ (14.4 g, 0.38 mol) over ca. 6 h and the reaction maintained at 0 °C for a further 2 h, whereupon the reaction was allowed to come to r.t. and the mixture stirred for a further 40 h. After concentration to ca. 300 mL, H₂O (1.0 L) was added cautiously and the mixture extracted with Et₂O (4 × 250 mL), the combined extracts washed with H₂O (3 × 250 mL), dried (MgSO₄) and evaporated in vacuo to afford compound **6** (61 g,

87%) as a yellow oil which was of sufficient purity for further reaction and was used directly in the deamination reaction without further purification.

¹H NMR (CDCl₃/TMS): δ = 6.28 (1 H, s), 6.14 (2 H, s), 2.45 (4 H, t, *J* = 5.0 Hz), 1.51 (4 H, m), 1.39 (2 H, m).

1,3-Dithiolium Iodide (**8**):

To an ice-cooled, mechanically stirred solution of Ac₂O (425 mL) under N₂ was cautiously added HPF₆ (60 wt% in H₂O, 190 g, 0.78 mol) (CAUTION: vigorous exothermic reaction!!) over ca. 2 h. To the ice-cooled solution of anhyd HPF₆ thus formed, was added dropwise over ca. 0.5 h a solution of crude **6** in anhyd Et₂O (500 mL), precipitating immediately the salt **7**. The mixture was diluted with anhyd Et₂O (500 mL), stirred for a further 0.5 h, the product was collected by filtration and washed with Et₂O (250 mL) affording salt **7** as an off-white solid. Purification was efficiently carried out by anion exchange (hexafluorophosphate to iodide). To a stirred solution of salt **7** in anhyd acetone (ca. 250 mL) under N₂ at 20 °C was added a solution of NaI (57 g, 0.38 mol) in anhyd acetone (ca. 100 mL) precipitating directly salt **8** as a bright yellow solid, which was collected by filtration and washed initially with cold anhyd acetone (50 mL) and then anhyd Et₂O (200 mL) (55 g, 73%); mp 140 °C (darkens at ca. 120 °C).

¹H NMR (DMSO-*d*₆/TMS): δ = 9.44 (2 H, d, *J* = 1.8 Hz), 9.34 (1 H, t, *J* = 1.8 Hz).

¹³C NMR (DMSO-*d*₆/TMS): δ = 181.3, 145.5.

Tetrathiafulvalene (**1**):⁷

To a mechanically stirred suspension of salt **8** (50 g, 0.21 mol) in anhyd MeCN (600 mL) under N₂ at 20 °C was added anhyd Et₃N (33 mL, 0.23 mol) dropwise over ca. 0.5 h and the mixture stirred for a further 1 h. H₂O (2.0 L) was added precipitating the product **1** as a flocculent orange solid, which was collected by filtration and washed with H₂O (250 mL). The crude solid was dissolved in CH₂Cl₂ (250 mL), washed with H₂O (2 × 250 mL), dried (MgSO₄) and evaporated in vacuo. The orange solid thus obtained was dissolved in boiling cyclohexane (ca. 1.0 L), treated with decolourising charcoal, filtered whilst hot and the filtrate immediately diluted with hexane (350 mL). The solution was chilled at 5 °C overnight, during which time the product crystallised as orange needles, which were collected by filtration, washed with cold hexane and dried (18.2 g, 85%). Further crops of material were obtained from the mother liquor by evaporation and recrystallisation (2.1 g, 10%); mp 119 °C (Lit.⁷ mp 119–119.5 °C).

¹H and ¹³C NMR data were identical with a commercial sample.

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- (13) The current price of TTF is £53.10 per gram (e.g., Aldrich catalogue, 1996–7).
- (14) After completion of this work, we were informed by Professor R. Elsenbaumer (University of Texas at Arlington) that a synthesis of TTF has been developed in his laboratory, starting from (Z)-1,2-dichloroethylene and the sodium salt derived from 4,5-bis(benzoylthio)-1,3-dithiole-2-thione. (R.L. Elsenbaumer, personal discussions, August 1996). We note that the current price of (Z)-1,2-dichloroethylene is £38.40 for 10 g (e.g., Aldrich catalogue 1996–7).
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